

## **REMARKS**

Claims 35-51 are pending in the present case. Reflecting the previously made election of species, Claims 35-37, 39-41, 43-48 and 51 are presently under examination. The Examiner has made a number of objections and rejections to the specification and claims. These will be addressed in the order presented in the Office Action.

## **OBJECTIONS**

### **1. Drawings.**

The Examiner has listed a number of drawings as being hard to read, or of poor quality. A set of formal drawings for the entire list of 104 drawings is included herewith. These drawings are formal versions of the drawings filed and do not contain new matter.

The Examiner has also indicated there is no label "Figure 96" in the drawings. This drawing is apparently missing from the USPTO file. Figure 96 was included with the application as filed. A formal version of the filed Figure 96 is included in the set of formal drawing included herewith. As this drawing was filed with the application, the formal drawing is not new matter.

### **2. Information Disclosure Statement**

Applicants note that the Examiner has received the IDS and Form 1449 filed on September 12, 2003. Clean copies of the cited references have been submitted in earlier filed cases. For example, copies of all references were supplied in parent Application Ser. No. 09/350,309. The Examiner is requested to review the references from this case.

### **3. Specification**

The Examiner states that it is unclear whether the present application claims the benefit of the parent applications recited on the cover page of the application. Applicants are not certain of the reason for this lack of clarity. The New Application Transmittal filed with the present application indicates that the present application claims the benefit of the patent applications and specifically identifies each parent case by its application serial number and relationship to the present application. However, Applicants note that the serial number of one parent application (08/759,038) contains a typographical error. This typographical error was inadvertent and is corrected in the amendment filed herewith. The application having the error in the serial number

was also identified by the correct U.S. Patent Number of the patent that issued from it.

In addition to this correction, the priority claim has been amended to provide the patent number of a parent case that was co-pending at the time of filing, but that has now issued.

The Examiner has asserted several inconsistencies between the drawings and the specification. First, the Examiner notes that the specification describes Figures 3A to 3G, 4A, 4B, 36A and 36B, and asserts that these drawings are not present. Applicants note that Drawings clearly labeled 3, 4 and 36 were filed in the present application and that the letter markings, also present on the drawings as filed, are used to indicate separate portions of the same drawing sheet, not separate sheets of drawings. Applicants submit herewith a complete set of formal drawings with 3A to 3G, 4A, 4B, 36A and 36B clearly marked. These markings correct informalities and are not new matter.

The Examiner has also noted that the application contains Figures 1A-1H, 2A-2C, 42A-42B, 59A-59E, and 88A-B, but asserts that the specification refers only to Figures 1, 2, 42, 59 and 88. The Description of Drawings is amended herein to refer to Figures 1A-1H, 2A-2C, 42A-42B, 59A-59E, and 88A-B. This amendment makes the specification consistent with the figure numbering and is not new matter.

#### **4. Claims**

Claim 35 is objected to for informalities in reciting "that can be, cleaved". Without acquiescing to the Examiner's arguments, and reserving the right to prosecute the same or similar claims in the future, Claim 35 is currently amended to recite "that can be cleaved."

Applicants have addressed each of the objections to the specification and claims and respectfully request that these objections be removed.

#### **REJECTIONS**

Claims 35-51 are pending in the present application and, as a result of species election, Claims 35-37, 39-41, 43-48 and 51 are presently under examination. The Examiner has rejected these Claims in an Office Action mailed April 20, 2004. For clarity, the rejections at issue are set forth by number in the order they are addressed herein:

1. Claims 35-37, 39-41, 43-48, and 51 stand rejected under 35. U.S.C. § 112, first paragraph

for failing to comply with the written description requirement, with respect to a) showing possession of the invention, b) providing enabling description, and c) particularly pointing out and distinctly claiming the subject matter of the invention.

2. Claims 35-37, 43-45, and 51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Goodman, *et al.*, U.S. Patent No. 4,994,368 ("Goodman").
3. Claims 39 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Goodman, in view of McKenzie, U.S. Patent No. 5,401,830 ("McKenzie").

Claims 36-41, 43-46, 48 and 51 are canceled without prejudice by the present amendment, rendering certain of these rejections moot. Applicants have cancelled these claims for business reasons, without acquiescing to the Examiner's arguments, and reserve the right to prosecute these or similar claims in the future.

Claims 35 and 47 are pending. Claim 35 has been amended to comprise all of the limitations of previous Claim 40.

**1. 35. U.S.C. § 112, first paragraph**

Claims 35-37, 39-41, 43-48, and 51 stand rejected under 35. U.S.C. § 112, first paragraph for failing to comply with the written description requirement, with respect to a) showing possession of the invention, b) providing enabling description, and c) particularly pointing out and distinctly claiming the subject matter of the invention. (Office Action page 3). Claims 36-41, 43-46, 48 and 51 are canceled without prejudice by the present amendment, rendering certain of these rejections moot. The rejection of remaining claims 35 and 47 are discussed herein below. Each of these § 112 rejections is discussed in the order presented above.

**a. The inventors were in possession of the invention at the time of filing**

Claim 35 relates to a method of detecting a target polynucleotide that comprises the steps of a) contacting a target polynucleotide having a first portion and a second portion immediately contiguous to one another with: i) an invader oligonucleotide, at least a part of which is capable of specifically hybridizing to the first portion of the target polynucleotide, ii) a probe oligonucleotide comprising a first region that is capable of specifically hybridizing to the second portion of the target polynucleotide and an unpaired region located adjacent to the first region,

and iii) a reagent that is capable of cleaving to release the unpaired region of the probe oligonucleotide when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide. In the present specification, INVADER oligonucleotides and probe oligonucleotides are disclosed throughout, *e.g.*, in Figures 28, 56, and 96, in numerous figures wherein these oligonucleotides are shown but not labeled as such, and in the text of the specification (see, *e.g.*, section II, on page 59, entitled "Detection of Specific Nucleic Acid Sequences Using 5' Nucleases In An INVADER-Directed Cleavage Assay").

The Examiner has raised specific questions about the phrases and terms "flap region," "reporter precursor," and "wherein the specific behavior as a function of time is non-linear." The other specific inquiries regarding the terms "quadratic" and "real time" are made moot by the cancellation of the claims reciting these terms.

The Examiner has asserted that the term "flap region" is not supported by the present specification and is thus new matter. (Office Action page 4). Without acquiescing to the Examiner's arguments and reserving the right to prosecute the original or a similar claim in the future, the term "flap" has been replaced in the present amendment with the term "unpaired." The term "unpaired" relates to the portions of oligonucleotides that are unpaired to the target as shown, *e.g.*, in Figure 96, schematically, and in Figure 99 and 103. Figures 96 and 99 show probe oligonucleotides comprising a 5' unpaired region. The term is used throughout the specification in reference to refer to non-hybridized portions of oligonucleotides and probes as used in the present invention. See, *e.g.*, the description of Figure 54 at page 220, lines 14-17, and lines 24-25. As such, the specification discloses probes having unpaired regions, as recited in Claim 35, and this term is not new matter.

The Examiner has asserted that the term "reporter precursor" is not supported by the present specification and is thus new matter. (Office Action page 4). Without acquiescing to the Examiner's arguments and reserving the right to prosecute the original or a similar claim in the future, the term "reporter precursor" has been replaced in the present amendment with the term "incomplete cleavage structure." The specification provides that an oligonucleotide released in a primary invasive cleavage reaction may be used as a component "to complete a cleavage structure to enable a secondary invasive cleavage reaction" (see, *e.g.*, page 112, lines 11-14, and

Figure 96). As such, the specification discloses incomplete cleavage structures for use in secondary cleavage reactions, such as is recited in Claim 35, and this term is not new matter.

The Examiner has asserted that the term "wherein the specific behavior as a function of time is non-linear" is not supported by the present specification. (Office Action, page 4). The present specification teaches that the yield of cleavage product, and therefore the signal, is a function of time of the reaction. See, *e.g.*, page 112, line 28 to page 113, line 7, which says explains that the yield of the first reaction step of the present invention has a yield Y, that is " the turnover rate, K, *multiplied by the time of the reaction, t* [*i.e.*,  $Y = (K)(t)$ ]" (*emphasis added*). The yield of the sequential reactions of the present invention is expressed as  $Y^n$ , where n is the number of cleavage reactions that performed in the series. Because Y is a function of time,  $Y^n$  is also a function of the time. As further explained in the specification (see, *e.g.*, page 117, line 28 to page 118, line 2), the accumulation of signal of the simple (non-sequential) assays is linear, while the accumulation of signal in the sequential cleavage reactions is exponential, *i.e.*, non-linear. Thus, the specification specifically teaches that the signal exhibits a specific behavior as a function of time (yield of product), wherein the specific behavior as a function of time is non-linear, and this term is not new matter.

Pending Claim 47 further recites that the signal is fluorescence or phosphorescence. The use of fluorescence and phosphorescence in the methods of the present invention is disclosed in the specification, *e.g.*, at page 13, lines 8-9. Thus, the specification specifically teaches the use of fluorescence and phosphorescence in the methods of the present invention, and this claim does not comprise new matter.

The present specification teaches each of the aspects of the presently claimed methods, showing that the inventors were in possession of the claimed invention at the time of filing and that these claims do not comprise new matter. Applicants therefore respectfully request that these rejections be withdrawn.

**b. The claims are enabled**

The Examiner asserts that, to the extent the claimed methods are not described in the instant disclosure, the claims are not enabled. (Office Action page 4). For the reasons recited



above, Applicants assert that the claimed methods are described in the instant specification and are enabled. Applicants therefore respectfully request that these rejections be withdrawn.

**c. The claims are not indefinite**

The Examiner asserts that the instant Claims are indefinite for several reasons:

1. Claim 35 stands rejected as vague and indefinite for lacking a method step correlating the determination of a signal that exhibits a specific behavior as a function of time with detection of the target nucleic acid. (Office Action page 5). For business reasons, and without acquiescing to the Examiner's arguments, Claim 35 has been amended to recite "wherein said signal that exhibits said specific behavior as a function of time is indicative of the presence of said target nucleic acid."

2. Claim 35 stands rejected for reciting "the cleaved flap region," which the Examiner asserts has insufficient antecedent basis. (Office Action page 5). As indicated above, the term "flap" has been replaced by the term "unpaired" in the present amendment. For business reasons, and without acquiescing to the Examiner's arguments, Claim 35 has been also amended to recite "iii) a reagent that is capable of cleaving to release the unpaired region of the probe oligonucleotide to produce a cleaved unpaired region . . ." As amended, Claim 35 provides antecedent basis for "the cleaved unpaired region."

3. Claim 35 stands rejected as vague and indefinite for the phrase "the cleaved flap region of the probe oligonucleotide and the reagent can come into contact with a reporter precursor to which the flap region of the probe oligonucleotide is capable of hybridizing to form a complex that can be, cleaved by the reagent to provide a reporter capable of being detected." The Examiner asserts that the first part of the phrase and the second part of the phrase do not correspond with each other. (Office Action page 5-6). As indicated above, the term "flap" has been replaced by the term "unpaired" in the present amendment. For business reasons, and without acquiescing to the Examiner's arguments, Claim 35 has been also amended to recite "the cleaved unpaired region of the probe oligonucleotide and the reagent can come into contact with an incomplete cleavage structure, to which the unpaired region of the probe oligonucleotide is

capable of hybridizing, to form a complex that can be cleaved by the reagent to provide a product capable of being detected. As amended, the claim clarifies that while the unpaired region of the probe is capable of hybridizing to the incomplete cleavage structure, the ~~cleaved~~ unpaired region of the probe of the probe oligonucleotide and the reagent can come into contact with an incomplete cleavage structure to form a complex that can be cleaved by the reagent.

Applicants have addressed each of the rejections made by the Examiner under 35 U.S.C. § 112, paragraph one. For the reasons recited above, Applicants assert that the requirements of § 112 are met and respectfully request that these rejections be removed.

## **2. 35 U.S.C. § 102**

### **The claims are not anticipated**

Claims 35-37, 43-45, and 51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Goodman, *et al*, U.S. Patent No. 4,994,368 ("Goodman"). Claims 36-37, 43-45 and 51 are canceled without prejudice in the present amendment, rendering this rejection moot with respect to these claims.

Claim 35 had been amended to recite "wherein said specific behavior as a function of time is non-linear", which previously appeared in dependent Claim 40. Claim 40, which depended from Claim 35 and which therefore included all of the limitations of Claim 35, was not rejected as being anticipated by Goodman. The Claim 35 as now amended comprises the limitations of Claim 40 and thus it appears that there should be no disagreement that the rejection should be withdrawn in view of this amendment.

## **3. 35 U.S.C. § 103**

### **The claims are not obvious**

Claims 39 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Goodman, in view of McKenzie, U.S. Patent No. 5,401,830 ("McKenzie"). (Office Action page 11). These claims are canceled without prejudice by the present amendment, rendering this rejection moot.

## **4. Claims Copied to Provoke an Interference**

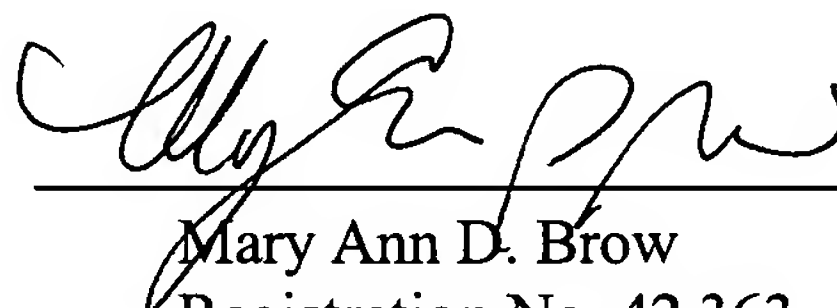
As previously noted, original claims Claims 35-50 were copied in order to provoke an interference. Applicants copied claims 1-13 from PCT Appln. No. PCT/US01/09579, published as WO 01/73127 A2, ("127") and claiming priority to U.S. Provisional Appln. 60/192,606 ("606"). On May 29, 2003, a U.S. application related to the '606 application, Appln. Ser No. 09/816,150 ("150"), was published as US 2003/0099941 A1. This application contains the same claims as the '127 publication and is currently in prosecution with Examiner Jeffrey Norman Fredman, in Group Art Unit 1634 (as indicated by a search of the USPTO PAIR database on October 20, 2003).

The claims of the present application are intended to encompass the subject matter claimed in the '150 application and to provoke an interference proceeding with the applicants of the '150 application.

## **CONCLUSION**

For the reasons set forth above, it is respectfully submitted that all objections and rejections should be removed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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